2013 AAAAI Annual Meeting, San Antonio, Texas, Seminar #4004 2/25/2013 Printed handout: How to assess and manage a child with multiple positive environmental and food allergy tests?

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Problem. Environmental and multiple positive food allergy tests can pose a diagnostic dilemma. This can occur in patients with atopic dermatitis or allergic rhinitis, in children with primary food allergies, or as a result of "panel testing" for allergies in children with no history of reactions. We will focus on differentiating primary from pollen-related food allergies as well as management of the latter.

The oral allergy syndrome (OAS) or pollen-food allergy syndrome (PFAS) [Boyce 2010] is referred to as type II food allergy that is secondary to airborne pollen sensitization, although not all patients have obvious seasonal allergy symptoms; these individuals can only be identified by objective testing for pollen sensitization. The most common signs and symptoms are pruritus, tingling, mild erythema, and subtle angioedema of the lips, oral mucosa, palate, and throat, sometimes accompanied by a sensation of throat swelling, oral papules, blisters. Symptoms occur while or shortly after (usually within five minutes of) ingesting the culprit uncooked fruits (including nuts) or raw vegetables and result from contact urticaria in the oropharynx caused by pollen-related proteins in these foods. Symptoms resolve promptly when the food is swallowed due to disruption of the structure of the allergen by gastric acid and proteolytic digestive enzymes. Only a small proportion of affected individuals experience systemic allergic reactions, although the disorder must be differentiated from more serious forms of classic, type I, primary food allergy. The term OAS has been imprecisely applied in the literature to describe oropharyngeal reactions also due to a variety of non-plant foods. It should be noted, that non-plant foods, such as cow's milk, egg, or seafood, however, do not cause oral allergy **syndrome**. OAS is the most common food allergy in adults but also affects a subgroup of children with pollen allergy. Risk factors for OAS include: sensitization to tree pollen, pollen-induced allergic rhinitis, and living in areas where pollen are prevalent. Differential diagnosis includes primary food allergy (these patients have no evidence of pollen sensitization or it is unrelated to their food allergy), contact urticaria, perioral dermatitis, GERD, EoE, burning mouth syndrome [burning rather than itching seen typically in middle-aged women].

OAS manifestations are highly variable. Particularly with fruits, patients may report that one variety of the food is more troublesome than another, or that the symptoms do not develop after every exposure. Certain varieties of apples have lower potential to induce OAS than others; Elise and Braeburn lower than Santana and Golden delicious.[Vlieg-Boerstra 2011] The peel of the fruit may be more allergenic than the pulp. Symptoms may increase during or following the pollen season due to seasonal boosting of pollen-IgE levels. In most cases, symptoms only develop when eating the raw, uncooked food. Cooking, baking, freezing, or even briefly microwaving raw fruits and vegetables is usually sufficient to alter the allergens responsible for OAS. Tree nuts and peanuts are an exception to this generalization, as roasted nuts can cause OAS. A few patients complain of nausea and abdominal discomfort, which may represent esophageal and gastric symptoms that develop before the allergen is fully degraded. True **systemic reactions** involve tissues that do not come into direct contact with undigested food. In a review of several studies, 9 % experienced associated symptoms outside of the gastrointestinal tract, and 1.7 % experienced anaphylactic shock [Ortolani 1993]. Patients who react to plant foods but do not report seasonal allergic rhinitis are at higher risk for systemic reactions, because they may have a primary food allergy, rather than OAS. Peanuts, tree nuts, peach, and mustard have been associated with higher rates of systemic reactions.

Pollen food associations *[Nowak-Wegrzyn 2012]*

Tree pollen

- Birch- Rosaceae and Betulaceae families: apple, peach, apricot, cherry, plum, pear, almond, hazelnut; Apiaceae family: carrot, celery, parsley, caraway, fennel, coriander, aniseed; Legumes: soy, peanut
- Plane tree (Sycamore): hazelnut, peach, apples, kiwi, peanut, corn, chickpea, lettuce, green beans

Weed pollen

- Ragweed: melon, Cucurbitaceae family: cantaloupe, honeydew, watermelon, zucchini, cucumber; bananas, avocado
- Mugwort: Apiaceae family (see above), bell pepper, black pepper, garlic, onion
- Cruciferae family: mustard, cauliflower, gabbage and broccoli

Grass pollen - melons, white potato, tomato, orange, Swiss chard, peanut

Specific syndromes associated with severe reactions: Celery-mugwort-spice syndrome, Mugwort-mustard syndrome, Latex fruit syndrome, Peach allergy related to lipid transfer protein (LTP) sensitization

Evaluation includes history, prick skin test (PST) with commercial extract for food and pollen, and fresh food prick-prick, serum specific IgE, and oral food challenge (OFC) as needed for unclear cases. The preferred method is prick-prick with fresh foods which is more sensitive than PST with commercial extracts which have low sensitivity for detecting sensitization to foods in OAS usually caused by unstable allergens that tend to destroy during extract production. An apple extract was positive in 2% vs prick-prick with fresh apple in 82% [Ortolani 1989]. Commercial extracts are useful to evaluate sensitization to tree nuts and legumes (peanut, hazelnut and pea), which contain stable allergens. Individuals positive to commercial extracts are more likely to experience systemic reactions. Serum IgE testing has not been systematically assessed in OAS. If there is no pollen sensitization, classic food allergy may be present. OFC is recommended when reactions occur to mixed foods, when testing fail to demonstrate sensitization to food, if unclear whether cooking eliminates symptoms (OFC to be performed with raw and cooked foods), or in those with systemic reactions to one food not previously exposed to a related food. Future diagnostic tests include basophil activation test and component resolved diagnostics (CRD), especially useful in differentiating sensitization to cross-reactive and primary sensitizing allergens. As an example, in peanut allergy: Ara h 8 is highly Bet v 1 cross-reactive, sensitization to Ara h 8 is associated with tolerance of peanut or very mild oral symptoms whereas Ara h 1, Ara h 2, Ara h 3, Ara h 6 are seed storage proteins that do not cross-react with pollen [Asarnoj

2012]; in hazelnut allergy: Cor a 1 is highly Bet v 1 cross-reactive, whereas Cor a 8 is an LTP and Cor a 9 is 11S globulin associated with systemic symptoms; in apple allergy Mal d 1 is Bet v 1 crossreactive, whereas sensitization to LTP is seen in severe symptoms.

Management and prognosis. The approach here represents authors' experience as there are no established guidelines. Patients are generally advised to avoid the specific **raw** fruits and vegetables as well as **roasted and raw** nuts that have caused symptoms in the past. Dehydrated forms may cause symptoms. Some patients choose to continue ingesting small amounts of the trigger food, with one small study reported improved OAS symptoms with continued intake of raw fruits [Kopac 2012]; however large amounts should be avoided such as in fruit shakes. Cooked forms need not be avoided unless patient has had oral symptoms or worsening atopic dermatitis due to them [Bohle 2006]. In those with history of systemic reaction it may be on the discretion of the patient and clinician whether also cooked forms should be avoided and tolerance to crossreactive foods needs to be carefully evaluated (foods tolerated may not need to be avoided; however those not part of diet need to be avoided or need an OFC). Indications for epinephrine include systemic reactions (seen in 2-10%) or reactions extending beyond the mouth cavity (i.e. dysphagia, significant throat discomfort), reactions of any severity to cooked plant foods, reactions to peanut, tree nuts or mustard, reactions to particular foods in geographic regions where food is associated with systemic reactions (i.e. peach, apple in the Mediterranean). Although there is some evidence that antihistamines may reduce symptoms of OAS, we do not recommend premedication with them. Immunotherapy may be beneficial. In an open trial of birch pollen SCIT in 49 adults with birch pollinosis, a significant reduction (50-95%) or a complete resolution of apple oral allergy symptoms was reported in 84% compared to non-treated controls ($P < 0.001$), associated with a marked reduction in skin reactivity against fresh apple.[Asero 1998] In a follow-up study, over 50% of subjects still tolerated apple at the 30-month follow-up after discontinuation of SCIT, although the majority showed evidence of re-sensitization by PST.[Asero 2003] A beneficial effect of birch SCIT was confirmed in a subset of subjects in subsequent clinical trials, in which oral allergy to apple was diagnosed with DBPCFC [Bucher 2004, Bolhaar 2004] as well as in an observational study of adults with plane tree pollinosis and OAS to hazelnut, walnut, lettuce, peach and cherry, treated with plane tree pollen SCIT.[Alonso 2007] However, a more rigorous study of 19 birch-allergic adults with hazelnut allergy, randomized to receive birch pollen SCIT or placebo for 12 months reported no change in the eliciting dose or symptom scores during the hazelnut DBPCFC.[van Hoffen 2011] Asero noted that most significant effects on OAS were observed in adults mono-sensitized to birch pollen and that for some subjects with OAS, IT doses higher that typically needed to produce improvement in birch pollen rhinitis may be necessary to improve PFAS. [Asero 2004] In a study using sublingual immunotherapy (SLIT) with birch pollen (maintenance dose equaling 4.5 µg Bet v 1 daily, a relatively low dose for SLIT), apple-OAS symptoms were not significantly reduced despite improved nasal provocation scores to pollen after 12 months of therapy.[Kinaciyan 2007] Clinical trials are needed to assess the efficacy of anti-IgE therapy. The prognosis is favorable without evidence of progression to systemic symptoms in the majority of patients although OAS tends to last life-long.

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